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Incorporation by coordination and release of the iron chelator drug deferiprone from zinc-based metal–organic frameworks†

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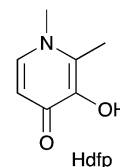
Andrew D. Burrows,^{*a} Monika Jurcic,^a Luke L. Keenan,^a Rebecca A. Lane,^a Mary F. Mahon,^{*a} Mark R. Warren,^b Harriott Nowell,^b Michael Paradowski^c and John Spencer^{*c}

A series of new zinc-based metal–organic framework materials has been prepared in which deferiprone is incorporated as a chelating ligand on infinite or tri-zinc secondary building units following deprotonation. Deferiprone is immediately released from the MOFs on treatments with 1 N hydrochloric acid or buffer, but slow release is observed in ethanoic acid.

Metal–organic frameworks (MOFs) are attracting considerable attention due to their potential for permanent porosity, and the consequent applications of this in areas as diverse as hydrogen storage, separations and heterogeneous catalysis.¹ Since the first report, in 2006, that bioactive molecules could be encapsulated within the pores of MOFs and released slowly,² there has been an increased focus on using MOFs to control drug delivery.³ As an alternative to including bioactive molecules as guests within pores of a pre-formed MOF, it is also possible to use this kind of molecule as a component of the framework itself.⁴ A number of examples have been reported, including those in which nicotinate,⁵ glutarate⁶ and theophylline⁷ have been incorporated as linkers. Many MOFs can be prepared with coordinatively unsaturated metal centres, and small bioactive molecules such as NO have been incorporated into such systems by coordination to these metal sites.⁸

In this communication, we report our initial studies on the inclusion into MOFs of the iron chelator drug deferiprone (Hdfp), which is used as an oral treatment for haemosiderosis (iron overload) that can occur as a consequence of regular blood transfusions required in the treatment of conditions such as thalassaemia major

and haemochromatosis.⁹ Deferiprone has high selectivity for Fe³⁺ over other cations, and it is used clinically in Europe and Asia as an orally active iron chelator. In addition, deferiprone possesses antioxidant properties protecting against oxidative stress,^{10,11} and recently it has been studied for potential application in the treatment of neurodegenerative diseases such as Alzheimer's.¹²



Despite its excellent bioavailability, deferiprone is known to have a number of side effects such as neutropenia and gastro-intestinal disorders. Moreover, it is metabolised (*ca.* 85%) by *O*-glucuronidation to a biologically inactive, non-iron chelating 3-*O*-glucuronide conjugate.¹³ Methods to reduce *O*-conjugation in order to reduce excretion are desirable, and incorporation within a framework material provides a potential means of achieving this.

We selected zinc-based MOFs for study, since the affinity of deferiprone for zinc(II) is known to be relatively low,¹⁴ and zinc MOFs generally decompose at low pH, which would be expected to trigger deferiprone release. The reaction of Zn(NO₃)₂·6H₂O with 1,4-benzenedicarboxylic acid (H₂bdc) and Hdfp in DMF at 100 °C for 24 h gave colourless block-shaped crystals, which were identified through single crystal X-ray analysis as [Zn₃(bdc)₂(dfp)₂]·2DMF **1**.†

Compound **1** has a three-dimensional network structure in which infinite zinc SBUs are bridged by the bdc linkers. The SBUs, shown in Fig. 1a, contain two independent zinc centres – Zn(1) lies on an inversion centres and is 6-coordinate, and bonded to four carboxylate and two dfp oxygen atoms, all from different ligands. Zn(2) is 5-coordinate, and bonded to two carboxylate and three dfp oxygen atoms, with one of the dfp ligands bidentate. The geometry of Zn(2) lies between square planar and trigonal bipyramidal ($\tau = 0.59^{15}$). Pairs of carboxylate ligands bridge between Zn(1) and Zn(2), whereas dfp, a deprotonated deferiprone, acts as a bidentate ligand on Zn(2), and a monodentate ligand to two Zn(1) centres. The infinite SBUs run along

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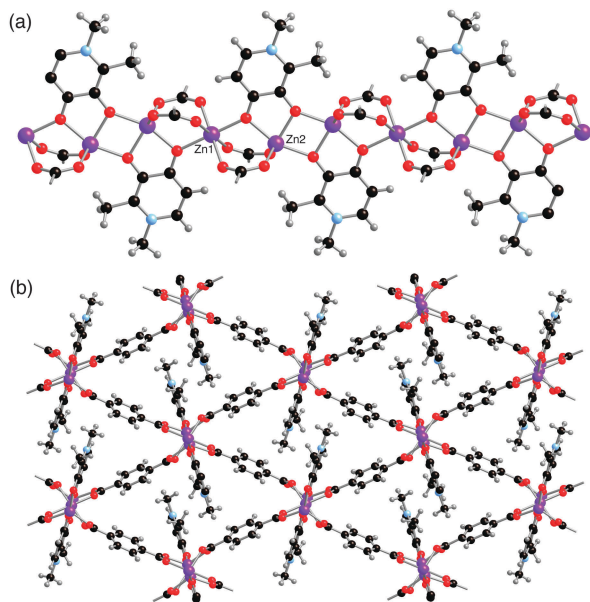


Fig. 1 The crystal structure of $[\text{Zn}_3(\text{bdc})_2(\text{dfp})_2]\cdot 2\text{DMF}$ **1**, showing (a) the infinite SBUs and (b) linking of the SBUs into the network.

the crystallographic *a*-axis, and are interconnected by the bdc linkers to generate rhomboidal pores, into which the dfp ligands project (Fig. 1b). The pores are also occupied by uncoordinated DMF molecules.

Changing the reaction solvent from DMF to water did not afford any MOF products, but changing it to a 5 : 1 mixture of ethanol and water led to colourless rhomboidal crystals that showed a different powder X-ray diffraction (PXRD) pattern to those of **1**. On analysis by single crystal X-ray crystallography, this product was identified as $[\text{Zn}_3(\text{bdc})_2(\text{dfp})_2(\text{H}_2\text{O})_2]$ **2**.

The structure of compound **2** is related to that of **1**, with infinite SBUs linked into a three-dimensional network by the bdc ligands. There are, however, subtle differences in the coordination geometries of the metal centres. Instead of pairs of carboxylate groups bridging between Zn(1) and Zn(2), as observed in **1**, only one carboxylate does this, and Zn(1), which lies on an inversion centre, maintains a 6-coordinate geometry by bonding to two water molecules. Zn(2) is coordinated to a bidentate carboxylate in addition to a bridging carboxylate, and as a consequence is 6-coordinate. As a result of this coordination, the infinite SBUs are considerably more puckered in **2** than they are in **1** (Fig. 2a), as witnessed by $\text{Zn}\cdots\text{Zn}\cdots\text{Zn}$ angles of 95.4° (cf. 152.9° for **1**). Hydrogen bonds are present between the water hydrogen atoms and both carboxylate and dfp oxygen atoms. Compound **2** exhibits similar rhomboidal pores to those in **1** (Fig. 2b), though these are flattened, which is consistent with the lack of inclusion of DMF. Use of a mixture of DMF and water as the solvent gave a mixture of **1** and **2**, as shown by PXRD.

The successful incorporation of deferiprone into the framework of the MOFs led us to consider the role of the bridging dicarboxylate, and to determine how the presence of functional groups would affect the structure. Consequently, the reaction between $\text{Zn}(\text{NO}_3)_2\cdot 6\text{H}_2\text{O}$ and deferiprone was carried out in the presence of 2-amino-1,4-benzenedicarboxylic acid ($\text{H}_2\text{bdc-NH}_2$) and 2,5-dihydroxy-1,4-benzenedicarboxylic acid ($\text{H}_2\text{bdc-(OH)}_2$) under similar conditions as those that gave the mixture of **1** and **2**.

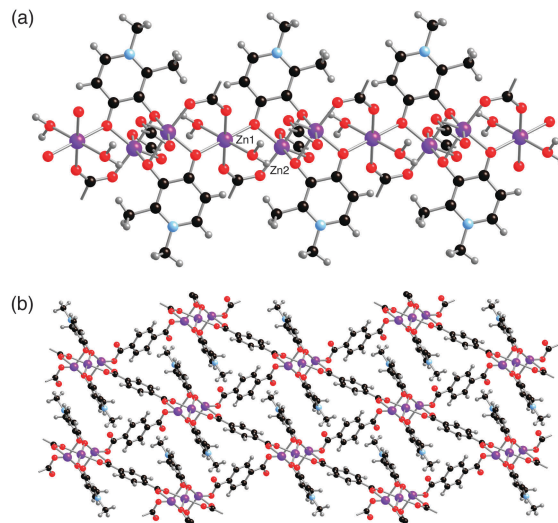


Fig. 2 The crystal structure of $[\text{Zn}_3(\text{bdc})_2(\text{dfp})_2(\text{H}_2\text{O})_2]$ **2**, showing (a) the infinite SBUs and (b) linking of the SBUs into the network.

In the case of $\text{H}_2\text{bdc-NH}_2$, two types of crystals were again observed in the product, and comparison of the PXRD patterns with those from the mixture of **1** and **2** suggested the products were the analogous compounds $[\text{Zn}_3(\text{bdc-NH}_2)_2(\text{dfp})_2]\cdot\text{DMF}$ **3** and $[\text{Zn}_3(\text{bdc-NH}_2)_2(\text{dfp})_2(\text{H}_2\text{O})_2]$ **4**. Compound **3** was further characterised by a single crystal X-ray analysis, which confirmed that it had a very similar network structure to that of **1**, with the amino groups disordered over two positions on the benzene ring (see ESI†).

In the case of $\text{H}_2\text{bdc-(OH)}_2$, only one crystal type was observed in the product. This was characterised crystallographically as $[\text{Zn}_3\{\text{bdc-(OH)}_2\}_2(\text{dfp})_2(\text{H}_2\text{O})_2]\cdot 2\text{DMF}$ **5**.† In contrast to **1–4**, compound **5** adopts a two-dimensional network structure, with individual $\text{Zn}_3(\text{O}_2\text{CR})_4(\text{dfp})_2(\text{H}_2\text{O})_2$ SBUs inter-connected into sheets by the dicarboxylate linkers. In the SBUs, Zn(1) and Zn(3) are each coordinated to five oxygen atoms, two from carboxylate groups, two from a bidentate dfp and a water molecule, with coordination geometries close to trigonal bipyramidal ($\tau = 0.75, 0.77$) whereas Zn(2), which lies on a two-fold rotation axis, is 6-coordinate, bonding to four carboxylate and two bridging dfp oxygen atoms (Fig. 3a). The water molecules serve to terminate the SBUs, and prevent aggregation into the infinite SBUs observed for **1–3**, though these are linked together through hydrogen bonds. The bdc-(OH)_2 linkers connect the SBUs into two-dimensional sheets (Fig. 3b), which contain rhomboidal pores into which the dfp ligands project, and the included DMF molecules are accommodated.

The tri-zinc units observed in **5**, and in an aggregated form in **1–4**, are a commonly observed motif in zinc MOFs, and have been observed in a number of compounds.^{16–19} In these frameworks, the SBU adopts a $\text{Zn}_3(\text{O}_2\text{CR})_6$ form, with carboxylate groups radiating out from the Zn_3 'spoke' at approximately 60° angles. In **1–5**, dfp linkers take the place of two of the carboxylates, so that the four carboxylate groups radiating from the SBU are at angles of 60° and 120° from each other, which in combination with the linear linkers generates the rhomboidal pores observed.

LCMS analyses showed that **1** gave no release of deferiprone on suspension in either DMSO or methanol, and was stable for more than 1 week in the presence of these solvents. Release of deferiprone

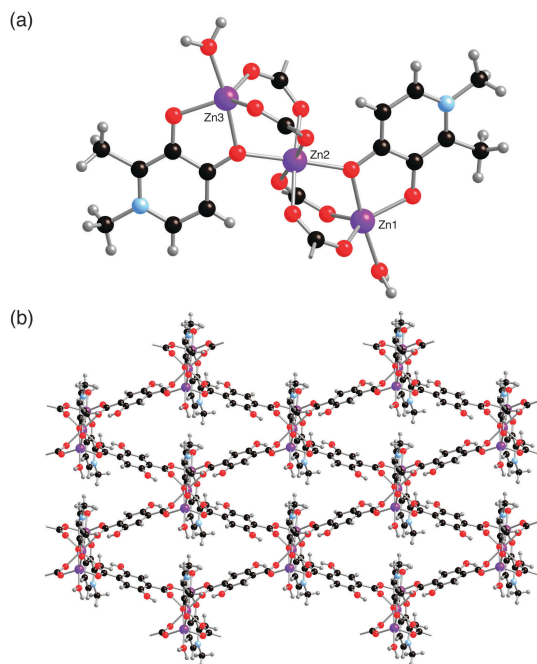
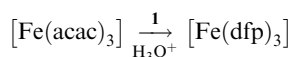


Fig. 3 The crystal structure of $[Zn_3(bdc(OH)_2)(dfp)_2(H_2O)_2] \cdot 2DMF$ **5**, showing (a) the tri-zinc SBUs and (b) linking of the SBUs into sheets.

from **1** was investigated by both acid digestion and ligand exchange reactions. Compound **1** dissolves in dilute hydrochloric acid, and following dissolution in $DCI-D_2O$ and $DMSO-d_6$, the 1H NMR spectrum, recorded straightaway, confirmed a 1:1 ratio of Hdfp and H_2bdc in solution. On treatment with hydrophilic solvents, *viz.* phosphate buffered saline (PBS buffer), HCl-PBS buffer (pH 5.5), 1 N HCl or saturated citric acid solution, the immediate release of deferiprone was also observed, as witnessed by elution in the LCMS at 0.52 min, with a corresponding m/z of 140.2 (calc. for H_2dfp^+ , 140.1). Intriguingly, a suspension of **1** in a 1:1 mixture of methanol and ethanoic acid (or neat ethanoic acid) led initially to only a trace of deferiprone (by LCMS), though after 20 min the UV intensity of the deferiprone has increased significantly, even more so after 55 min. This demonstrates proof of concept for the potential future employment of MOFs as drug release platforms, although the release properties of the MOFs need optimisation. It should be stressed that MOFs themselves are insoluble, and can only be dissolved by decomposition into the component parts. As such, they can be considered as potential depots for deferiprone. The cytotoxicity of deferiprone is well established²⁰ and H_2bdc , released with it, has low toxicity;²¹ indeed, the drug oxycodone is sometimes delivered as a salt of this acid.

Treatment of a suspension of **1** with $[Fe(acac)_3]$ (Hacac = pentane-2,4-dione) in DMF at 40 °C for 48 h gave no reaction, however on acidification of the solution with dilute hydrochloric acid, deferiprone was released as the MOF decomposes and is trapped in the form of $[Fe(df_p)_3]$, as witnessed by mass spectrometry of the product ($m/z = 471.1076$, calc. 471.1093 for $[M + H]^+$, 493.0921, calc. 493.0912 for $[M + Na]^+$).



In conclusion, we have demonstrated that following deprotonation, deferiprone can be included as a ligand in zinc metal-organic frameworks, forming both two- and three-dimensional networks. It adopts a bidentate coordination geometry, reducing the connectivity of the SBUs, generating frameworks with rhomboidal pores. Deferiprone can be released from the MOFs by treatment with PBS or acid, with the rate of release affected by the nature of the acid employed. Current studies are aimed at broadening the type of MOF structures that can incorporate deferiprone as a means of controlling their drug release properties, and results will be reported in due course.

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Notes and references

† Crystal data **1**: $C_{18}H_{19}N_2O_7Zn_{1.5}$, $M = 473.41$, monoclinic, $P2_1/n$, $a = 9.7750(1)$ Å, $b = 18.9580(2)$ Å, $c = 11.4690(1)$ Å, $\beta = 111.354(1)^\circ$, $U = 1979.46(3)$ Å³, $Z = 4$, $D_c = 1.589$ g cm⁻³, $\mu(Mo-K\alpha) = 1.874$ mm⁻¹, final $R_1 = 0.0248$, $wR_2 = 0.0593$ for $I > 2\sigma(I)$, $R_1 = 0.0288$, $wR_2 = 0.0618$ for all data, GoF = 1.054. **2**: $C_{30}H_{28}N_2O_{14}Zn_3$, $M = 836.65$, triclinic, $P\bar{1}$, $a = 8.127(3)$ Å, $b = 9.909(3)$ Å, $c = 11.353(4)$ Å, $\alpha = 107.182(2)^\circ$, $\beta = 90.439(4)^\circ$, $\gamma = 113.787(3)^\circ$, $U = 790.9(5)$ Å³, $Z = 1$, $D_c = 1.757$ g cm⁻³, $\mu(Mo-K\alpha) = 2.331$ mm⁻¹, final $R_1 = 0.0348$, $wR_2 = 0.0986$ for $I > 2\sigma(I)$, $R_1 = 0.0401$, $wR_2 = 0.1010$ for all data, GoF = 1.013. **3**: $C_{33}H_{33}N_5O_{13}Zn_3$, $M = 903.76$, monoclinic, $P2_1/n$, $a = 9.7350(1)$ Å, $b = 18.8760(3)$ Å, $c = 11.5940(2)$ Å, $\beta = 108.578(1)^\circ$, $U = 2020.18(5)$ Å³, $Z = 2$, $D_c = 1.486$ g cm⁻³, $\mu(Mo-K\alpha) = 1.832$ mm⁻¹, final $R_1 = 0.0355$, $wR_2 = 0.1094$ for $I > 2\sigma(I)$, $R_1 = 0.0479$, $wR_2 = 0.1149$ for all data, GoF = 1.088. **5**: $C_{36}H_{42}N_4O_{20}Zn_3$, $M = 1046.85$, hexagonal, $P6_522$, $a = 11.2503(1)$ Å, $b = 11.2503(1)$ Å, $c = 59.7860(11)$ Å, $U = 6553.27(15)$ Å³, $Z = 6$, $D_c = 1.592$ g cm⁻³, $\mu(Mo-K\alpha) = 1.717$ mm⁻¹, final $R_1 = 0.0357$, $wR_2 = 0.0728$ for $I > 2\sigma(I)$, $R_1 = 0.0426$, $wR_2 = 0.0763$ for all data, GoF = 0.893.

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